Clinical trial results:
A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Newly Diagnosed Multiple Myeloma

Summary

EudraCT number	2013-000326-54
Trial protocol	FR BE
Global end of trial date	24 June 2022

Results information

Result version number	v1 (current)
This version publication date	07 July 2023
First version publication date	07 July 2023

Trial information

Trial identification

Sponsor protocol code	C16014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01850524
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, MA, United States, 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to provide continued access to ixazomib and/or lenalidomide to participants who are continuing to have clinical benefit and to continue collecting relevant safety data to monitor safety in participants with Newly Diagnosed Multiple Myeloma (NDMM) who are not eligible for stem cell transplant.

Protection of trial subjects:

Each participant signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 262
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Japan: 59
Country: Number of subjects enrolled	Belgium: 73
Country: Number of subjects enrolled	Korea, Republic of: 31
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	United States: 147
Country: Number of subjects enrolled	Canada: 122
Worldwide total number of subjects	705
EEA total number of subjects	335

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	19
From 65 to 84 years	658
85 years and over	28

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 238 investigative sites in multiple countries from 29 April 2013 to 24 June 2022.

Pre-assignment

Screening details:

Participants with newly diagnosed multiple myeloma were enrolled in 1:1 ratio to receive ixazomib or placebo in addition to the background therapy of Lenalidomide and Dexamethasone (LenDex) in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + LenDex

Arm description:

Participants who were randomly assigned to receive placebo matching capsule single oral dose on Days 1, 8 and 15 along with standard regimen of LenDex (lenalidomide 25 mg capsules orally on Days 1-21 and dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22) for the first 18 cycles (each cycle was of 28 days). Following Cycle 18, participants received 3.0 mg ixazomib matching placebo capsule as single oral dose on Days 1, 8 and 15 along with lenalidomide 10 mg capsules orally on Days 1-21 in each 28-day cycle until progressive disease or unacceptable toxicity, whichever comes first up to end of study (up to approximately 109 months).

Arm type	Experimental
Investigational medicinal product name	Placebo matching Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ixazomib 4.0 mg capsule single oral dose on Days 1, 8 and 15 for the first 18 cycles (each cycle was of 28 days).

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22 for the first 18 cycles (each cycle was of 28 days).

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide 25 mg capsules orally on Days 1-21.

Arm title	Ixazomib + LenDex

Arm description:

Participants who were randomly assigned to receive Ixazomib 4.0 mg capsule single oral dose on Days 1, 8 and 15 along with standard regimen of LenDex (lenalidomide 25 mg capsules orally on Days 1-21 and dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22) for the first 18 cycles (each cycle was of 28 days). Following Cycle 18, participants received 3.0 mg ixazomib capsule as single oral dose on Days 1, 8 and 15 along with lenalidomide 10 mg capsules orally on Days 1-21 in each 28-day cycle until progressive disease or unacceptable toxicity, whichever comes first up to end of study (up to approximately 109 months).

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ixazomib 4.0 mg capsule single oral dose on Days 1, 8 and 15 for the first 18 cycles (each cycle was of 28 days). Following cycle 18 participants received 3.0 mg ixazomib capsule as a single oral dose on Days 1, 8 and 15 in each 28-day cycle.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22 for the first 18 cycles (each cycle was of 28 days).

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide 25 mg capsules orally on Days 1-21 for the first 18 cycles (each cycle was of 28 days). Following Cycle 18, Participants received lenalidomide 10 mg capsules orally on Days 1-21 in each 28-day cycle.

Number of subjects in period 1	Placebo + LenDex	Ixazomib + LenDex
Started	354	351
Intent-to-Treat (ITT) Population	354	351
Completed Study Treatment Per Protocol	283	284
Per Protocol (PP) Population	293	296
Participants With Exposure of ≥ 19 Cycle	189	191
Response-evaluable Population	347	335
Completed	183	178
Not completed	171	173
Withdrawal by Subject	24	22
Lost to follow-up	5	10

Reason not specified	142	141

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + LenDex
Reporting group description:	
Participants who were randomly assigned to receive placebo matching capsule single oral dose on Days 1, 8 and 15 along with standard regimen of LenDex (lenalidomide 25 mg capsules orally on Days 1-21 and dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22) for the first 18 cycles (each cycle was of 28 days). Following Cycle 18, participants received 3.0 mg ixazomib matching placebo capsule as single oral dose on Days 1, 8 and 15 along with lenalidomide 10 mg capsules orally on Days 1-21 in each 28-day cycle until progressive disease or unacceptable toxicity, whichever comes first up to end of study (up to approximately 109 months).	
Reporting group title	Ixazomib + LenDex
Reporting group description:	
Participants who were randomly assigned to receive Ixazomib 4.0 mg capsule single oral dose on Days 1, 8 and 15 along with standard regimen of LenDex (lenalidomide 25 mg capsules orally on Days 1-21 and dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22) for the first 18 cycles (each cycle was of 28 days). Following Cycle 18, participants received 3.0 mg ixazomib capsule as single oral dose on Days 1, 8 and 15 along with lenalidomide 10 mg capsules orally on Days 1-21 in each 28-day cycle until progressive disease or unacceptable toxicity, whichever comes first up to end of study (up to approximately 109 months).	

Reporting group values	Placebo + LenDex	Ixazomib + LenDex	Total
Number of subjects	354	351	705
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	73.7	73.5	
standard deviation	± 5.91	± 6.53	-
Gender categorical Units: Subjects			
Female	172	179	351
Male	182	172	354
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	14	12	26
Not Hispanic or Latino	340	337	677
Unknown or Not Reported	0	2	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	2	3

Asian	52	44	96
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	13	11	24
White	285	291	576
Unknown or Not Reported	3	2	5
Height			
'n= 341, 339'. 'n' indicates number of participants available for analysis at baseline			
Units: centimetre			
arithmetic mean	164.7	164.3	
standard deviation	± 10.04	± 10.13	-
Body Surface Area (BSA)			
'n= 341, 339'. 'n' indicates number of participants available for analysis at baseline. BSA = square root of (height x weight/3600)			
Units: square metre			
arithmetic mean	1.789	1.810	
standard deviation	± 0.2306	± 0.2456	-
Weight			
Units: kilogram(s)			
arithmetic mean	70.53	72.67	
standard deviation	± 15.353	± 16.995	-

End points

End points reporting groups

Reporting group title	Placebo + LenDex

Reporting group description:

Participants who were randomly assigned to receive placebo matching capsule single oral dose on Days 1, 8 and 15 along with standard regimen of LenDex (lenalidomide 25 mg capsules orally on Days 1-21 and dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22) for the first 18 cycles (each cycle was of 28 days). Following Cycle 18, participants received 3.0 mg ixazomib matching placebo capsule as single oral dose on Days 1, 8 and 15 along with lenalidomide 10 mg capsules orally on Days 1-21 in each 28-day cycle until progressive disease or unacceptable toxicity, whichever comes first up to end of study (up to approximately 109 months).

Reporting group title	Ixazomib + LenDex

Reporting group description:

Participants who were randomly assigned to receive Ixazomib 4.0 mg capsule single oral dose on Days 1, 8 and 15 along with standard regimen of LenDex (lenalidomide 25 mg capsules orally on Days 1-21 and dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22) for the first 18 cycles (each cycle was of 28 days). Following Cycle 18, participants received 3.0 mg ixazomib capsule as single oral dose on Days 1, 8 and 15 along with lenalidomide 10 mg capsules orally on Days 1-21 in each 28-day cycle until progressive disease or unacceptable toxicity, whichever comes first up to end of study (up to approximately 109 months).

Subject analysis set title	Placebo + LenDex (Exposure Up to 18 Cycles)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who were randomly assigned to receive placebo matching capsule single oral dose on Days 1, 8 and 15 along with standard regimen of LenDex (lenalidomide 25 mg capsules orally on Days 1-21 and dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22) up to 18 cycles (each cycle was of 28 days).

Subject analysis set title	Ixazomib+ LenDex (Exposure Up to 18 Cycles)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who were randomly assigned to receive Ixazomib 4.0 mg capsule single oral dose on Days 1, 8 and 15 along with standard regimen of LenDex (lenalidomide 25 mg capsules orally on Days 1-21 and dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22) up to 18 cycles (each cycle was of 28 days).

Subject analysis set title	Placebo + LenDex (Exposure ≥19 Cycles)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who were randomly assigned to receive placebo matching capsule single oral dose on Days 1, 8 and 15 along with standard regimen of LenDex (lenalidomide 25 mg capsules orally on Days 1-21 and dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22) up to 18 cycles (each cycle was of 28 days). Following Cycle 18, participants received 3.0 mg ixazomib placebo matching capsule as single oral dose on Days 1, 8 and 15 along with lenalidomide 10 mg capsules orally on Days 1-21 in each 28-day cycle until progressive disease or unacceptable toxicity, whichever comes first up to end of study (up to approximately 109 months).

Subject analysis set title	Ixazomib + LenDex (Exposure ≥19 Cycles)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who were randomly assigned to receive Ixazomib 4.0 mg placebo matching capsule single oral dose on Days 1, 8 and 15 along with standard regimen of LenDex (lenalidomide 25 mg capsules orally on Days 1-21 and dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22) up to 18 cycles (each cycle was of 28 days). Following Cycle 18, participants received 3.0 mg ixazomib capsule as single oral dose on Days 1, 8 and 15 along with lenalidomide 10 mg capsules orally on Days 1-21 in each 28-day cycle until progressive disease or unacceptable toxicity, whichever comes first up to end of study (up to approximately 109 months).

Subject analysis set title	Ixazomib
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who were randomly assigned to receive Ixazomib 4.0 mg capsules orally once on Days

1,8,15 and lenalidomide 25 mg capsules orally on days 1-21 and dexamethasone 40 mg tablets orally on Days 1,8, 15 and 22, during every 28-day cycle for the first 18 cycles.
After Cycle 18 dexamethasone was discontinued and participants continued to receive ixazomib capsule and lenalidomide at reduced doses until progressive disease or unacceptable toxicity, whichever comes first, up to end of study (up to approximately 109 months).

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time from the date of randomization to the date of first documentation of progressive disease (PD) or death due to any cause according to International Myeloma Working Group (IMWG) criteria whichever occurs first. PD required one of the following: Increase of >=25% from nadir in: Serum M-component and/or (the absolute increase must be >=0.5 g/dL); Urine M-component and/or (the absolute increase must be >=200 mg/24 hours); in participants without measurable serum and urine M-protein levels: the difference between involved and uninvolved free light chain (FLC) levels (absolute increase must be > 10 mg/dL); Bone marrow plasma cell percentage: the absolute % must be >10%; development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas; hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.85 mmol/L). ITT population included all participants who were randomized.

End point type	Primary

End point timeframe:

Up to approximately 79 months

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	351		
Units: months				
median (confidence interval 95%)	21.8 (19.65 to 30.78)	35.3 (26.45 to 43.70)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + LenDex v Ixazomib + LenDex
Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.073 [1]
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.676
upper limit	1.018

Notes:

[1] - Log-rank test is stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomization to the date of death. Participants without documented death at the time of analysis are censored at the date last known to be alive. ITT population included all participants who were randomized. 99999 indicates that Median and Upper limit of Confidence Interval (CI) was not estimable due to censoring of participants as most participants were still alive during last contact.

End point type	Secondary

End point timeframe:

From the date of randomization to death due to any cause (Up to approximately 9 years)

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	351		
Units: months				
median (confidence interval 95%)	99999 (58.71 to 99999)	99999 (63.18 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ixazomib + LenDex v Placebo + LenDex
Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.988 [3]
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.998
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.261

Notes:

[2] - Hazard ratio is based on an Unadjusted Cox’s proportional hazard regression model is stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.
[3] - Log-rank test is stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

Secondary: Pain Response Rate as Assessed by the Brief Pain Inventory- Short Form (BPI-SF) and Analgesic Use

End point title	Pain Response Rate as Assessed by the Brief Pain Inventory-Short Form (BPI-SF) and Analgesic Use

End point description:

Pain response rate was defined as percentage of participants with pain response. Pain response was defined as the occurrence of at least a 30% reduction from baseline in BPI-SF worst pain score over the

last 24 hours without an increase in analgesic use for 2 consecutive measurements > 28 days apart, were reported. Brief Pain Inventory - Short Form (m-BPI-SF) is a participant rated 11-point Likert rating scale ranged from 0 (no pain) to 10 (worst pain imaginable). Percentages are rounded off to the nearest single decimal. ITT population included all participants who were randomized. 'N' indicates overall number of participants with baseline worst pain score>=4 as assessed by m-BPI-SF.

End point type	Secondary

End point timeframe:

Up to approximately 9 years

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	190		
Units: percentage of participants				
number (not applicable)	51.3	50.5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + LenDex v Ixazomib + LenDex
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.9195 [5]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.656
upper limit	1.463

Notes:

[4] - Odds ratio > 1 favors Ixazomib+LenDex versus LenDex alone.

[5] - Logistic regression model with prognostic factor: age (<75 years vs >=75) and ISS (stage I or II vs stage III).

Secondary: Complete Response (CR) Rate

End point title	Complete Response (CR) Rate

End point description:

CR rate was defined as the percentage of participants who achieve CR assessed by an IRC relative to the intent-to-treat (ITT) population during the treatment period. Percentage of participants with CR, as assessed by IMWG disease assessment criteria were reported. CR was defined as negative immunofixation of serum and urine along with the disappearance of any soft tissue plasmacytomas and <5 % plasma cells (PC's) in bone marrow. ITT population included all participants who were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 9 years

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	351		
Units: percentage of participants				
number (not applicable)	14	26		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + LenDex v Ixazomib + LenDex
Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.001 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.43
upper limit	3.09

Notes:

[6] - Odds ratio and confidence interval are based on logistic regression model with treatment group as categorical predictor variable,age(<75 years vs >=75), ISS(stage I or II vs stage III),and BPI-SF worst pain score(<4 vs >=4)at screening as covariates.
[7] - CMH test is stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR was defined as the percentage of participants who achieved CR + partial response (PR) + very good partial response (VGPR) (including sCR) or better relative to the ITT population during treatment period. CR was defined as negative immunofixation of serum and urine along with the disappearance of any soft tissue plasmacytomas and <5 % PC's in bone marrow. PR was defined as ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% along with ≥50% reduction in the size of soft tissue plasmacytomas. VGPR was defined as ≥90% in serum M-component plus urine M-component <100 mg/24. sCR is defined as stringent complete response. Percentages are rounded off to nearest whole numbers. ITT population included all participants who were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 9 years

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	351		
Units: percentage of participants				
number (not applicable)	80	82		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + LenDex v Ixazomib + LenDex
Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.436 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.7

Notes:

[8] - Odds ratio and confidence interval are based on logistic regression model with treatment group as categorical predictor variable,age(<75 years vs >=75), ISS(stage I or II vs stage III),and BPI-SF worst pain score(<4 vs >=4)at screening as covariates.

[9] - CMH test is stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was defined as the time from the date of randomization to the first documentation of PR or better, as measured by IMWG criteria. ITT population included all participants who were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 9 years

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	351		
Units: months				
median (confidence interval 95%)	1.87 (1.15 to 1.87)	1.02 (0.99 to 1.08)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + LenDex v Ixazomib + LenDex
Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.001 [11]
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.402
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.185
upper limit	1.659

Notes:

[10] - Hazard ratio is based on an unadjusted Cox's proportional hazard regression model stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

[11] - Log-rank test is stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

Secondary: Progression Free Survival (PFS)-2

End point title	Progression Free Survival (PFS)-2

End point description:

PFS2 was defined as the time from the date of randomization to the date of documentation of disease progression on the subsequent line of anticancer therapy, as assessed by the investigator in accordance with IMWG criteria, or death due to any cause, whichever occurs first. ITT population included all participants who were randomized. 99999 indicated that Upper limit of CI was not estimable to due insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Up to approximately 9 years

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	351		
Units: months				
median (confidence interval 95%)	52.2 (45.21 to 61.90)	63.2 (54.70 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + LenDex v Ixazomib + LenDex
Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.189 [13]
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.859
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.684
upper limit	1.078

Notes:

[12] - Hazard ratio is based on an unadjusted Cox's proportional hazard regression model stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.
[13] - Log-rank test is stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

Time to progression was defined as the time from randomization to the date of first documented disease progression. ITT population included all participants who were randomized.

End point type	Secondary

End point timeframe:

Up to approximately 9 years

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	351		
Units: months				
median (confidence interval 95%)	26.8 (21.22 to 37.91)	45.8 (31.84 to 56.25)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + LenDex v Ixazomib + LenDex

Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.008 [15]
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.738
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.589
upper limit	0.925

Notes:

[14] - Hazard ratio is based on an unadjusted Cox's proportional hazard regression model stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

[15] - Log-rank test is stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response was measured as the time from the date of first documentation of PR or better to the date of first documented progression (PD) for responders, as measured by IMWG criteria. Response-evaluable population was defined as all participants in the ITT population who receive at least 1 dose of any study drug, have measurable disease at baseline, and at least 1 post baseline response assessment assessed by an IRC. Overall number of participants analyzed are the number of responders. 99999 indicates that Upper limit of CI was not estimable as participants without documentation of PD at the date of last response assessment that is stable disease (SD) or better were censored.

End point type	Secondary

End point timeframe:

Up to approximately 9 years

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	287		
Units: months				
median (confidence interval 95%)	37.5 (25.69 to 50.27)	50.6 (39.98 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shifts From Baseline to Worst Value in Eastern Cooperative Oncology Group (ECOG) Performance Score

End point title	Number of Participants With Shifts From Baseline to Worst Value in Eastern Cooperative Oncology Group (ECOG) Performance Score

End point description:

Eastern Cooperative Oncology Group (ECOG) scale score ranged from 0 to 5, where 0 indicated normal activity and 5 indicated death. The data is reported for those categories where at least 1 participant had worst post-baseline value for each ECOG score. Safety population is defined as all participants who receive at least 1 dose of any study drug. 'N' indicates overall number of participants available for analysis.

End point type	Secondary

End point timeframe:

Up to approximately 9 years

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	344	340		
Units: participants				
Baseline Score 0, Post-Baseline Score 0	23	23		
Baseline Score 0, Post-Baseline Score 1	57	52		
Baseline Score 0, Post-Baseline Score 2	20	23		
Baseline Score 0, Post-Baseline Score 3	2	10		
Baseline Score 1, Post-Baseline Score 0	1	1		
Baseline Score 1, Post-Baseline Score 1	96	104		
Baseline Score 1, Post-Baseline Score 2	72	57		
Baseline Score 1, Post-Baseline Score 3	18	9		
Baseline Score 1, Post-Baseline Score 4	6	4		
Baseline Score 2, Post-Baseline Score 1	12	8		
Baseline Score 2, Post-Baseline Score 2	28	35		
Baseline Score 2, Post-Baseline Score 3	7	11		
Baseline Score 2, Post-Baseline Score 4	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a participant administered a medicinal investigational drug. The untoward medical occurrence does not necessarily have to have a causal relationship with treatment. An SAE is any untoward medical occurrence that results in death; is life-threatening; requires inpatient hospitalization or prolongation of present hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect or is a medically important event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require intervention to prevent one of other outcomes listed in definition above, or involves suspected transmission via a medicinal product of an infectious agent.Safety population= participants who receive at least 1 dose of any study drug. Data for safety is summarized as per duration of exposure to study treatment (exposure up to 18 cycles; exposure ≥19 cycles)

End point type	Secondary

End point timeframe:

From the date of randomization through 30 days after the last dose of study drug up to end of study (up

to approximately 9 years)

End point values	Placebo + LenDex (Exposure Up to 18 Cycles)	Ixazomib+ LenDex (Exposure Up to 18 Cycles)	Placebo + LenDex (Exposure ≥19 Cycles)	Ixazomib + LenDex (Exposure ≥19 Cycles)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	160	163	189	191
Units: participants				
TEAEs	160	163	189	191
SAEs	105	119	119	125

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Serum Chemistry and Hematology Laboratory Values Based on Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants With Abnormal Serum Chemistry and Hematology Laboratory Values Based on Treatment-emergent Adverse Events (TEAEs)

End point description:

Laboratory values assessment included serum chemistry and hematology. Serum chemistry assessment - blood urea nitrogen(BUN), creatinine, bilirubin(total), urate, lactate dehydrogenase, phosphate, albumin, alkaline phosphatase(ALP), aspartate aminotransferase(AST), alanine aminotransferase(ALT), glucose, sodium, potassium, calcium, chloride, carbon dioxide(CO2), magnesium, thyroid stimulating hormone(TSH). Hematology assessment - hemoglobin, hematocrit, platelet(count), leukocytes with differential neutrophils(ANC). Participants with abnormal serum chemistry and hematology values reported as TEAEs are reported. TEAEs: events that occurred after administration of first dose of any agent in study drug regimen and through 30 days after last dose of any agent in study drug regimen. Safety population:participants who receive at least 1 dose of any study drug. Data for safety is summarized as per duration of exposure to study treatment(exposure up to 18 cycles; exposure ≥19 cycles).

End point type	Secondary

End point timeframe:

From the date of randomization through 30 days after the last dose of study drug up to end of study (up to approximately 9 years)

End point values	Placebo + LenDex (Exposure Up to 18 Cycles)	Ixazomib+ LenDex (Exposure Up to 18 Cycles)	Placebo + LenDex (Exposure ≥19 Cycles)	Ixazomib + LenDex (Exposure ≥19 Cycles)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	160	163	189	191
Units: participants				
Hypokalaemia	16	33	33	39
Blood creatinine increased	9	6	12	16
Hypophosphataemia	2	9	3	9

Hypomagnesaemia	8	6	11	15
Hyponatraemia	7	10	8	7
Hyperglycaemia	4	7	16	6
Hypocalcaemia	13	6	12	4
Hyperkalaemia	3	7	3	3
Alanine aminotransferase increased	1	1	4	10
Iron deficiency	2	1	2	7
Hypercalcaemia	6	2	1	5
Creatinine renal clearance decreased	2	1	7	4
Hypoalbuminaemia	5	2	1	3
Aspartate aminotransferase increased	1	0	3	5
Hyperuricaemia	2	2	1	2
Anaemia	57	53	52	58
Thrombocytopenia	15	34	14	24
Neutropenia	36	15	48	39
Neutrophil count decreased	11	5	13	18
Platelet count decreased	6	6	4	15
Lymphopenia	0	7	2	4
Febrile neutropenia	5	7	2	2
Leukopenia	3	6	4	2
International normalised ratio increased	1	4	0	4
Pancytopenia	2	3	1	2
Iron deficiency anaemia	1	1	1	4
White blood cell count decreased	5	1	3	2
Lymphocyte count decreased	1	2	3	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health-Related Quality of Life (HRQOL) Measured by European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC-QLQ)-C30 Scale Total Score

End point title	Change From Baseline in Health-Related Quality of Life (HRQOL) Measured by European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC-QLQ)-C30 Scale Total Score

End point description:

EORTC-QLQ-C30 scale (30 items) was used to assess HRQOL. Subscale with individual items:physical functioning items 1-5, role functioning items 6-7, emotional functioning items 21-24, cognitive functioning items 20, 25, social functioning items 26-27, quality of life items 29-30, fatigue items 10, 12, 18, nausea and vomiting items 14-15, pain items 9, 19, dyspnoea item 8, insomnia item 11, appetite loss item 13, constipation item 16, diarrhoea item 17, financial difficulties item 28. Raw scores were converted into scale scores ranging from 0 to 100. Functional scales and global health status(GHS) scale:higher scores=better HRQOL. Symptom scales:lower scores=better HRQOL. Positive change in functional and global health status scale=improvement; negative change for symptom scales=improvement. ITT population. 'N' indicates overall number of participants available for analyses. 'n' indicates number of participants available for analysis at given timepoint.

End point type	Secondary

End point timeframe:

Baseline to approximately 9 years

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353	351		
Units: score on a scale				
arithmetic mean (standard deviation)				
GHS/QOL Baseline (n= 352, 351)	55.2 (± 23.53)	56.4 (± 23.66)		
GHS/QOL End of Treatment (EOT) (n= 220, 217)	-2.2 (± 26.03)	-4.1 (± 29.48)		
Physical Functioning: Baseline (n= 353, 350)	60.0 (± 28.73)	61.4 (± 27.96)		
Physical Functioning: EOT (n= 223, 217)	1.7 (± 26.81)	0.3 (± 28.23)		
Role Functioning: Baseline (n= 352, 350)	54.9 (± 36.52)	56.5 (± 36.60)		
Role Functioning: EOT (n= 223, 217)	-0.3 (± 36.25)	-1.8 (± 36.74)		
Emotional Functioning: Baseline (n= 353, 351)	73.5 (± 23.09)	72.6 (± 24.84)		
Emotional Functioning: EOT (n= 222, 217)	-2.4 (± 21.70)	-0.5 (± 24.35)		
Cognitive Functioning: Baseline (n= 353, 351)	77.8 (± 22.97)	78.3 (± 25.92)		
Cognitive Functioning: EOT (n= 222, 217)	-3.2 (± 25.14)	-5.1 (± 24.70)		
Social Functioning: Baseline (n= 351, 351)	69.1 (± 32.54)	69.5 (± 33.01)		
Social Functioning: EOT (n= 220, 217)	-2.9 (± 31.56)	-2.5 (± 36.57)		
Fatigue: Baseline (n= 353, 350)	44.6 (± 28.30)	40.8 (± 27.69)		
Fatigue: EOT (n= 223, 218)	-2.3 (± 27.75)	4.5 (± 31.04)		
Pain: Baseline (n= 353, 351)	45.6 (± 34.04)	42.5 (± 33.51)		
Pain: EOT (n= 225, 218)	-5.5 (± 33.77)	-3.5 (± 34.55)		
Nausea and Vomiting: Baseline (n= 353, 350)	7.1 (± 15.75)	8.1 (± 18.49)		
Nausea and Vomiting: EOT (n= 224, 218)	-0.5 (± 19.80)	1.6 (± 25.22)		
Dyspnoea: Baseline (n= 352, 350)	26.2 (± 30.25)	24.0 (± 29.35)		
Dyspnoea: EOT (n= 222, 217)	-3.6 (± 30.86)	2.8 (± 33.83)		
Insomnia: Baseline (n= 353, 350)	30.3 (± 30.31)	34.3 (± 32.20)		
Insomnia: EOT (223, 217)	-1.5 (± 35.06)	-1.1 (± 36.06)		
Appetite Loss: Baseline (n= 353, 350)	25.4 (± 33.14)	25.5 (± 33.04)		
Appetite Loss: EOT (n= 223, 218)	-1.2 (± 37.42)	3.4 (± 38.65)		
Constipation: Baseline (n= 352, 351)	25.9 (± 32.94)	24.9 (± 32.19)		
Constipation: EOT (n= 222, 218)	-7.1 (± 39.03)	-5.7 (± 35.83)		
Diarrhoea: Baseline (n= 352, 351)	8.2 (± 19.45)	6.7 (± 16.58)		
Diarrhoea: EOT (n= 221, 217)	10.7 (± 27.72)	18.3 (± 31.73)		
Financial Difficulties: Baseline (n= 352, 351)	12.5 (± 24.04)	12.3 (± 24.03)		
Financial Difficulties: EOT (n= 220, 216)	2.0 (± 27.42)	0.8 (± 25.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HRQOL Measured by EORTC-QLQ-MY20 Scale

End point title	Change From Baseline in HRQOL Measured by EORTC-QLQ-MY20 Scale

End point description:

EORTC QLQ-MY20 was a validated questionnaire to assess the overall quality of life in participants with multiple myeloma. The scale has 20 questions. Subscale and individual items include future perspective items 18-20, body image item 17, disease symptoms items 1-6, side effects of treatment items 7-16. Raw scores are averaged, and transformed to 0-100 scale, where higher score is better quality of life. Positive change indicates improvement. ITT population included all participants who were randomized. 'N' indicates overall number of participants available for analyses. 'n' indicates the number of participants available for analysis at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline to approximately 9 years

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	352	350		
Units: score on a scale				
arithmetic mean (standard deviation)				
Disease Symptoms: Baseline (n= 352, 350)	30.3 (± 23.76)	29.2 (± 22.97)		
Disease Symptoms: EOT (222, 215)	-3.1 (± 20.74)	-5.3 (± 22.44)		
Side-Effects: Baseline (352, 350)	18.0 (± 14.53)	17.6 (± 15.04)		
Side-Effects: EOT (n= 222, 214)	1.7 (± 14.52)	3.3 (± 15.91)		
Body Image: Baseline (n= 346, 346)	81.7 (± 27.67)	81.2 (± 29.11)		
Body Image: EOT (n= 215, 207)	-7.8 (± 31.93)	-2.3 (± 29.66)		
Future Perspective: Baseline (n= 350, 349)	57.3 (± 25.95)	55.0 (± 28.47)		
Future Perspective: EOT (220, 211)	4.4 (± 24.85)	6.0 (± 25.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: OS in High-risk Population Carrying Del(17p), t(4;14), or t(14;16) Mutations

End point title	OS in High-risk Population Carrying Del(17p), t(4;14), or t(14;16) Mutations

End point description:

OS was defined as the time from the date of randomization to the date of death, as assessed in high-risk population carrying del(17p), t(4;14), or t(14;16) mutations. High risk category includes t(4;14), t(14;16), or del(17) abnormalities. ITT population included all participants who were randomized. 'N' indicates overall number of participants from the high-risk category. 99999 indicated that upper range of CI was not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

From the date of randomization to death due to any cause (Up to approximately 9 years)

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	60		
Units: months				
median (confidence interval 95%)	43.1 (33.84 to 57.82)	39.0 (25.43 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

OS in High-risk Population Carrying Del(17p), Amp(1q21), t(4;14), or t(14;16) Mutations

Comparison groups	Placebo + LenDex v Ixazomib + LenDex
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.662 [17]
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.118
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.678
upper limit	1.845

Notes:

[16] - Hazard ratio is based on an unadjusted Cox’s proportional hazard regression model stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

[17] - Log-rank test is stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

Secondary: PFS in High-risk Population Carrying Del(17p), t(4;14), or t(14;16) Mutations

End point title	PFS in High-risk Population Carrying Del(17p), t(4;14), or t(14;16) Mutations

End point description:

PFS was defined as the time from the date of randomization to the date of first documentation of progressive disease based on central laboratory results and IMWG criteria as evaluated by an independent review committee (IRC) or death due to any cause, whichever occurs first, as assessed in high-risk population carrying del(17p), t(4;14), or t(14;16) mutations. ITT population included all participants who were randomized. 'N' indicates overall number of participants from the high-risk category.

End point type	Secondary

End point timeframe:

Up to approximately 9 years

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	60		
Units: months				
median (confidence interval 95%)	17.5 (12.12 to 20.30)	22.4 (12.16 to 42.84)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: PFS in High-risk Population Carrying del(17p), t(4;14), or t(14;16) Mutations	
Comparison groups	Placebo + LenDex v Ixazomib + LenDex
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.271 [19]
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.466
upper limit	1.24

Notes:

[18] - Hazard ratio is based on an unadjusted Cox's proportional hazard regression model stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

[19] - Log-rank test is stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

Secondary: Time to Pain Progression

End point title	Time to Pain Progression

End point description:

Time to pain progression was assessed as the time from randomization to the date of initial progression classification. Pain progression was defined as the occurrence of 1 of the following and confirmed by 2 consecutive evaluations (To qualify as progression, the participant must have a BPI-SF worst pain score > 4 during pain progression): 1) a ≥ 2 point and 30% increase from Baseline in BPI-SF worst pain score without an increase in analgesic use, or 2) a 25% or more increase in analgesic use from Baseline without a decrease in BPI-SF worst pain score from Baseline. Brief Pain Inventory - Short Form (m-BPI-SF) is a participant rated 11-point Likert rating scale ranged from 0 (no pain) to 10 (worst pain imaginable). ITT population included all participants who were randomized. 99999 indicates that Median, upper limit and/or lower limit of CI was not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Up to approximately 9 years

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	354	351		
Units: months				
median (confidence interval 95%)	47.1 (30.88 to 99999)	99999 (57.59 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Time to Pain Progression	
Comparison groups	Placebo + LenDex v Ixazomib + LenDex
Number of subjects included in analysis	705
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.26 [21]
Method	Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.661
upper limit	1.12

Notes:

[20] - Hazard ratio is based on an unadjusted Cox’s proportional hazard regression model stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

[21] - Log-rank test is stratified by age (<75 years vs >=75), ISS (stage I or II vs stage III), and BPI-SF worst pain score (<4 vs >=4) at screening.

Secondary: Percentage of Participants With MRD-Negative Status as Assessed by Flow Cytometry

End point title	Percentage of Participants With MRD-Negative Status as Assessed by Flow Cytometry

End point description:

The absence of minimal residual disease (MRD negativity) was tested in all participants who achieve a CR and maintained it until Cycle 18, using bone marrow aspirates. Response-evaluable population includes all participants in the ITT population who receive at least 1 dose of any study drug, have measurable disease at baseline, and at least 1 post baseline response assessment assessed by an IRC.

End point type	Secondary

End point timeframe:

Up to approximately 9 years

End point values	Placebo + LenDex	Ixazomib + LenDex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	335		
Units: percentage of participants				
number (not applicable)	50	59		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Maximum Plasma Concentration for Ixazomib

End point title	Cmax: Maximum Plasma Concentration for Ixazomib

End point description:

Pharmacokinetic (PK) analysis population is defined as subjects with at least one PK sample that was collected and analyzed. 'N' indicates overall number of participants available for analyses. 'n' indicates number of participants available for analysis at the given timepoint.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: Post-dose at multiple timepoints up to 4 hours; Pre-dose at Cycle 1 Day 14, Cycles 2-3 Day 1 and Day 14, Cycles 4-11 Day 1 (Each cycle length = 28 days)

End point values	Ixazomib			
Subject group type	Subject analysis set			
Number of subjects analysed	331			
Units: millilitre(s)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1: 1 Hour Post-dose (n= 331)	44.745 (± 35.9404)			
Cycle 1 Day 1: 4 Hours Post-dose (n= 320)	16.253 (± 17.0407)			
Cycle 1 Day 14: Pre-dose (n= 327)	7.867 (± 15.4420)			
Cycle 2 Day 1: Pre-dose (n= 320)	2.664 (± 2.2770)			
Cycle 2 Day 14: Pre-dose (n= 302)	8.521 (± 14.7411)			
Cycle 3 Day 1: Pre-dose (n= 300)	2.763 (± 1.6318)			
Cycle 3 Day 14: Pre-dose (n= 275)	8.490 (± 17.6720)			
Cycle 4 Day 1: Pre-dose (n= 284)	3.284 (± 6.1116)			
Cycle 5 Day 1: Pre-dose (n= 270)	3.594 (± 13.2046)			
Cycle 6 Day 1: Pre-dose (n= 260)	2.603 (± 1.5242)			
Cycle 7 Day 1: Pre-dose (n= 258)	2.598 (± 1.4658)			
Cycle 8 Day 1: Pre-dose (n= 251)	2.539 (± 1.5549)			

Cycle 9 Day 1: Pre-dose (n= 242)	2.593 (± 2.0867)			
Cycle 10 Day 1: Pre-dose (n= 238)	2.536 (± 1.7431)			
Cycle 11 Day 1: Pre-dose (n=224)	2.667 (± 4.5448)			
Cycle 12 Day 1: Pre-dose (n=217)	2.686 (± 1.8949)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With New or Worsening of Existing Skeletal-related Events (SREs)

End point title	Percentage of Participants With New or Worsening of Existing Skeletal-related Events (SREs)

End point description:

SRE is defined as new fractures [including vertebral compression fractures], irradiation of or surgery on bone, or spinal cord compression. Safety population is defined as all participants who receive at least 1 dose of any study drug. Data for safety is summarized as per the duration of exposure to study treatment (exposure up to 18 cycles; exposure ≥19 cycles).

End point type	Secondary

End point timeframe:

From the date of randomization through 30 days after the last dose of study drug up to end of study (up to approximately 9 years)

End point values	Placebo + LenDex (Exposure Up to 18 Cycles)	Ixazomib+ LenDex (Exposure Up to 18 Cycles)	Placebo + LenDex (Exposure ≥19 Cycles)	Ixazomib + LenDex (Exposure ≥19 Cycles)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	160	163	189	191
Units: percentage of participants				
number (not applicable)	14	10	28	25

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of randomization through 30 days after the last dose of study drug up to end of study (approximately 9 years)

Adverse event reporting additional description:

Safety population.4 participants randomized to placebo received ixazomib during study and were included in ixazomib arm for safety population. 1 participant randomized to each arm withdrew from study and was not included. Data for safety is summarized per the duration of exposure to study treatment (exposure up to 18 cycles;exposure ≥19 cycles).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

Reporting group title	Placebo + LenDex (Exposure Up to 18 Cycles)

Reporting group description: -

Reporting group title	Placebo + LenDex (Exposure ≥19 Cycles)

Reporting group description:

Participants who were randomly assigned to receive Placebo were administered ixazomib 4.0 mg placebo matching capsule single oral dose on Days 1, 8 and 15 along with standard regimen of LenDex (lenalidomide 25 mg capsules orally on Days 1-21 and dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22) up to 18 cycles (each cycle was of 28 days). Following Cycle 18, participants received 3.0 mg ixazomib placebo matching capsule as single oral dose on Days 1, 8 and 15 along with lenalidomide 10 mg capsules orally on Days 1-21 in each 28-day cycle until progressive disease or unacceptable toxicity, whichever comes first up to end of study (up to approximately 109 months).

Reporting group title	Ixazomib + LenDex (Exposure ≥19 Cycles)

Reporting group description:

Participants who were randomly assigned to receive Ixazomib were administered ixazomib 4.0 mg placebo matching capsule single oral dose on Days 1, 8 and 15 along with standard regimen of LenDex (lenalidomide 25 mg capsules orally on Days 1-21 and dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22) up to 18 cycles (each cycle was of 28 days). Following Cycle 18, participants received 3.0 mg ixazomib capsule as single oral dose on Days 1, 8 and 15 along with lenalidomide 10 mg capsules orally on Days 1-21 in each 28-day cycle until progressive disease or unacceptable toxicity, whichever comes first up to end of study (up to approximately 109 months).

Reporting group title	Ixazomib+ LenDex (Exposure Up to 18 Cycles)

Reporting group description:

Participants who were randomly assigned to receive Ixazomib were administered ixazomib 4.0 mg capsule single oral dose on Days 1, 8 and 15 along with standard regimen of LenDex (lenalidomide 25 mg capsules orally on Days 1-21 and dexamethasone 40 mg tablets orally on Days 1, 8, 15 and 22) up to 18 cycles (each cycle was of 28 days).

Serious adverse events	Placebo + LenDex (Exposure Up to 18 Cycles)	Placebo + LenDex (Exposure ≥19 Cycles)	Ixazomib + LenDex (Exposure ≥19 Cycles)
Total subjects affected by serious adverse events			
subjects affected / exposed	105 / 160 (65.63%)	119 / 189 (62.96%)	125 / 191 (65.45%)
number of deaths (all causes)	107	63	63
number of deaths resulting from adverse events	17	5	7
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Adenocarcinoma of colon			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute erythroid leukaemia			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 160 (0.63%)	6 / 189 (3.17%)	12 / 191 (6.28%)
occurrences causally related to treatment / all	0 / 1	6 / 6	8 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder adenocarcinoma			

subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal adenoma			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung carcinoma cell type unspecified stage I			

subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large granular lymphocytosis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sarcomatoid carcinoma			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	4 / 191 (2.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			

subjects affected / exposed	1 / 160 (0.63%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Plasma cell leukaemia			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer recurrent			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell cancer of the renal pelvis and ureter			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 160 (0.63%)	4 / 189 (2.12%)	5 / 191 (2.62%)
occurrences causally related to treatment / all	1 / 1	3 / 4	5 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral artery stenosis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			

subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	3 / 160 (1.88%)	5 / 189 (2.65%)	4 / 191 (2.09%)
occurrences causally related to treatment / all	3 / 3	5 / 5	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 160 (0.63%)	2 / 189 (1.06%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			

subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 160 (1.25%)	1 / 189 (0.53%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	5 / 160 (3.13%)	2 / 189 (1.06%)	3 / 191 (1.57%)
occurrences causally related to treatment / all	4 / 8	1 / 3	1 / 4
deaths causally related to treatment / all	1 / 2	0 / 1	0 / 0
Complication associated with device			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Fatigue			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			

subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated hernia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Non-cardiac chest pain			

subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	2 / 160 (1.25%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 160 (1.88%)	3 / 189 (1.59%)	4 / 191 (2.09%)
occurrences causally related to treatment / all	2 / 3	1 / 4	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent-graft endoleak			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	3 / 191 (1.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 3
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Testicular oedema			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystocele			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute respiratory failure			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	2 / 160 (1.25%)	0 / 189 (0.00%)	3 / 191 (1.57%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	7 / 160 (4.38%)	5 / 189 (2.65%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	7 / 7	6 / 6	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis aspiration			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paranasal cyst			

subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 160 (0.63%)	1 / 189 (0.53%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 160 (0.63%)	5 / 189 (2.65%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 1	1 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			

subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obsessive thoughts			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device breakage			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device loosening			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blast cells present			

subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcus test positive			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	3 / 160 (1.88%)	2 / 189 (1.06%)	4 / 191 (2.09%)
occurrences causally related to treatment / all	1 / 3	0 / 2	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture displacement			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			

subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 160 (0.63%)	1 / 189 (0.53%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic injury			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis radiation			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	3 / 191 (1.57%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 160 (0.00%)	3 / 189 (1.59%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 160 (0.63%)	4 / 189 (2.12%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			

subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb traumatic amputation			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			

subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention postoperative			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	3 / 160 (1.88%)	2 / 189 (1.06%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	1 / 3	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			

subjects affected / exposed	1 / 160 (0.63%)	3 / 189 (1.59%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 1	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	3 / 160 (1.88%)	3 / 189 (1.59%)	4 / 191 (2.09%)
occurrences causally related to treatment / all	0 / 3	0 / 3	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	2 / 160 (1.25%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	3 / 191 (1.57%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive heart disease			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			

subjects affected / exposed	5 / 160 (3.13%)	2 / 189 (1.06%)	3 / 191 (1.57%)
occurrences causally related to treatment / all	3 / 6	1 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 160 (0.63%)	1 / 189 (0.53%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 160 (1.25%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			

subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	2 / 160 (1.25%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prosthetic cardiac valve malfunction			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Demyelinating polyneuropathy			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicobrachial syndrome			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	2 / 160 (1.25%)	1 / 189 (0.53%)	3 / 191 (1.57%)
occurrences causally related to treatment / all	2 / 2	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral infarction			

subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intraventricular haemorrhage			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperaesthesia			

subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hemiplegia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			

subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Senile dementia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peroneal nerve palsy			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal claudication			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			

subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 160 (0.63%)	5 / 189 (2.65%)	4 / 191 (2.09%)
occurrences causally related to treatment / all	0 / 1	1 / 5	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thalamic infarction			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thalamus haemorrhage			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 160 (1.25%)	2 / 189 (1.06%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	1 / 2	1 / 2	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	2 / 160 (1.25%)	2 / 189 (1.06%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	2 / 2	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	1 / 160 (0.63%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amaurosis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	0 / 160 (0.00%)	3 / 189 (1.59%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eyelid ptosis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic nerve sheath haemorrhage			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dental caries			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			

subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haematoma			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	7 / 191 (3.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	6 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			

subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric volvulus			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis haemorrhagic			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			

subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			

subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periodontal disease			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctalgia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	4 / 191 (2.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal prolapse			

subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			

subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermal cyst			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis allergic			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug eruption			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens-Johnson syndrome			

subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash erythematous			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash macular			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash papular			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic epidermal necrolysis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic skin eruption			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	8 / 160 (5.00%)	2 / 189 (1.06%)	3 / 191 (1.57%)
occurrences causally related to treatment / all	2 / 9	0 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Focal segmental glomerulosclerosis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myeloma cast nephropathy			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	3 / 160 (1.88%)	0 / 189 (0.00%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 160 (1.88%)	2 / 189 (1.06%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone lesion			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondrocalcinosis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondrocalcinosis pyrophosphate			

subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kyphosis			
subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture pain			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crystal arthropathy			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	4 / 160 (2.50%)	4 / 189 (2.12%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 4	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sarcopenia			

subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 160 (0.63%)	2 / 189 (1.06%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteolysis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporotic fracture			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			

subjects affected / exposed	2 / 160 (1.25%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bartholinitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 160 (0.00%)	5 / 189 (2.65%)	4 / 191 (2.09%)
occurrences causally related to treatment / all	0 / 0	1 / 5	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess jaw			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis bacterial			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 160 (0.63%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 160 (1.25%)	2 / 189 (1.06%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	2 / 2	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			

subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis infective			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis staphylococcal			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	3 / 160 (1.88%)	3 / 189 (1.59%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 4	1 / 3	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	3 / 191 (1.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 160 (0.63%)	2 / 189 (1.06%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal oesophagitis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			

subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 160 (0.63%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 160 (1.25%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 160 (0.63%)	2 / 189 (1.06%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			

subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	2 / 160 (1.25%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	16 / 160 (10.00%)	13 / 189 (6.88%)	22 / 191 (11.52%)
occurrences causally related to treatment / all	7 / 18	7 / 13	15 / 26
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia parainfluenzae viral			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			

subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia haemophilus			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	2 / 191 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis Escherichia coli			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			

subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	4 / 160 (2.50%)	4 / 189 (2.12%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	3 / 4	2 / 5	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Sepsis syndrome			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 160 (0.63%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis aspergillus			

subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	4 / 160 (2.50%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	2 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 3	0 / 0	0 / 0
Superinfection bacterial			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic shock syndrome staphylococcal			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	2 / 160 (1.25%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 160 (0.63%)	3 / 189 (1.59%)	6 / 191 (3.14%)
occurrences causally related to treatment / all	0 / 1	1 / 4	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral uveitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	5 / 191 (2.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypervolaemia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	2 / 160 (1.25%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 160 (0.63%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	4 / 160 (2.50%)	1 / 189 (0.53%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	2 / 160 (1.25%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 160 (0.63%)	1 / 189 (0.53%)	4 / 191 (2.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 160 (0.63%)	2 / 189 (1.06%)	3 / 191 (1.57%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 160 (0.00%)	2 / 189 (1.06%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	1 / 191 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 160 (0.00%)	0 / 189 (0.00%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	1 / 160 (0.63%)	1 / 189 (0.53%)	0 / 191 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ixazomib+ LenDex (Exposure Up to 18 Cycles)		

Total subjects affected by serious adverse events			
subjects affected / exposed	119 / 163 (73.01%)		
number of deaths (all causes)	95		
number of deaths resulting from adverse events	21		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute erythroid leukaemia			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bowen's disease			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma pancreas			

subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gallbladder adenocarcinoma				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colorectal adenoma				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colorectal adenocarcinoma				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic myeloid leukaemia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric cancer				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to liver				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung carcinoma cell type unspecified stage I				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large granular lymphocytosis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic malignant melanoma				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Papillary thyroid cancer				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sarcomatoid carcinoma				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Plasma cell myeloma				
subjects affected / exposed	3 / 163 (1.84%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
Plasma cell leukaemia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer recurrent				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of lung				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transitional cell cancer of the renal pelvis and ureter				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Superficial spreading melanoma stage unspecified				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				

Peripheral artery stenosis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral arterial occlusive disease				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic stenosis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Embolism				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypovolaemic shock				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				

subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Phlebitis				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis limb				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	5 / 163 (3.07%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 2			
Complication associated with device				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Fatigue				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Generalised oedema				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperthermia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Incarcerated hernia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inflammation				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza like illness				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	3 / 163 (1.84%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Stent-graft endoleak				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Systemic inflammatory response syndrome				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				

subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Testicular oedema			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cystocele			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	5 / 163 (3.07%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			

subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Acute respiratory distress syndrome				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute pulmonary oedema				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Asthma				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	4 / 163 (2.45%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumonitis aspiration				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paranasal cyst				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infiltration				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	3 / 163 (1.84%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Delirium				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hallucination				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Obsessive thoughts				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device breakage				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device loosening				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				

Blood creatinine increased				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood alkaline phosphatase increased				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blast cells present				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
International normalised ratio increased				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcus test positive				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Accidental overdose				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Hip fracture				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fracture displacement				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ankle fracture				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic injury				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervical vertebral fracture				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis radiation				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				

subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin laceration				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Limb traumatic amputation				

subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention postoperative			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			

subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Angina pectoris			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	3 / 163 (1.84%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			

subjects affected / exposed	4 / 163 (2.45%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	1 / 4			
Hypertensive heart disease				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiomyopathy				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	3 / 163 (1.84%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Ischaemic cardiomyopathy				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Myocardial infarction				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus bradycardia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prosthetic cardiac valve malfunction				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Demyelinating polyneuropathy				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cervicobrachial syndrome				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haematoma				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Embolic stroke				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intraventricular haemorrhage				

subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxic-ischaemic encephalopathy				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperaesthesia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hemiplegia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lacunar infarction				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lethargy				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Senile dementia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peroneal nerve palsy				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Posterior reversible encephalopathy syndrome				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorder				

subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal claudication				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	5 / 163 (3.07%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Thalamic infarction				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Thalamus haemorrhage				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	5 / 163 (3.07%)			
occurrences causally related to treatment / all	5 / 7			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				

subjects affected / exposed	4 / 163 (2.45%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	4 / 163 (2.45%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Angle closure glaucoma			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Amaurosis			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cataract			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eyelid ptosis			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Optic nerve sheath haemorrhage			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal adhesions			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dental caries			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal wall haematoma			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal hernia			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	8 / 163 (4.91%)		
occurrences causally related to treatment / all	7 / 10		
deaths causally related to treatment / all	0 / 0		
Diverticular perforation			

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric volvulus				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis haemorrhagic				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal ischaemia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pancreatitis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				

subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Periodontal disease				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Proctalgia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Retroperitoneal haemorrhage				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal haemorrhage				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal prolapse				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Volvulus				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholelithiasis				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis chronic				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangitis acute				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic cirrhosis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic function abnormal				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Decubitus ulcer				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dermal cyst				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dermatitis allergic				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Drug eruption				

subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Drug reaction with eosinophilia and systemic symptoms				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stevens-Johnson syndrome				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash erythematous				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash macular				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Rash maculo-papular				
subjects affected / exposed	4 / 163 (2.45%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Rash papular				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Toxic epidermal necrolysis				

subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Toxic skin eruption				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	5 / 163 (3.07%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Chronic kidney disease				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Focal segmental glomerulosclerosis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myeloma cast nephropathy				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nephritis				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Arthritis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthralgia				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone lesion				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bone pain				

subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chondrocalcinosis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chondrocalcinosis pyrophosphate				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mobility decreased				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Kyphosis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemarthrosis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fracture pain				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Crystal arthropathy				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	3 / 163 (1.84%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Sarcopenia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal osteoarthritis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteolysis				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoporotic fracture				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Synovitis				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal stenosis				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis perforated				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bartholinitis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	3 / 163 (1.84%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Abscess jaw				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis bacterial				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis				

subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Campylobacter gastroenteritis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bursitis infective				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis staphylococcal				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis E				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				

subjects affected / exposed	4 / 163 (2.45%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Fungal oesophagitis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Erysipelas				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Endocarditis				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Parainfluenzae virus infection				

subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural infection				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	22 / 163 (13.50%)			
occurrences causally related to treatment / all	11 / 28			
deaths causally related to treatment / all	1 / 1			
Lower respiratory tract infection viral				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia parainfluenzae viral				

subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia legionella			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia influenzal			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia haemophilus			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia pneumococcal			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Pulmonary sepsis			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pseudomonal sepsis			

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostatitis Escherichia coli				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	4 / 163 (2.45%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	1 / 1			
Sepsis syndrome				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	3 / 163 (1.84%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				

subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis aspergillus				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	4 / 163 (2.45%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 1			
Superinfection bacterial				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth infection				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxic shock syndrome staphylococcal				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	3 / 163 (1.84%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral uveitis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypervolaemia				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Diabetic ketoacidosis				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				

subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	6 / 163 (3.68%)			
occurrences causally related to treatment / all	4 / 9			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypomagnesaemia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hypocalcaemia				
subjects affected / exposed	0 / 163 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malnutrition				

subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo + LenDex (Exposure Up to 18 Cycles)	Placebo + LenDex (Exposure ≥19 Cycles)	Ixazomib + LenDex (Exposure ≥19 Cycles)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	159 / 160 (99.38%)	189 / 189 (100.00%)	191 / 191 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 160 (5.63%)	18 / 189 (9.52%)	29 / 191 (15.18%)
occurrences (all)	10	20	32
Hypotension			
subjects affected / exposed	12 / 160 (7.50%)	11 / 189 (5.82%)	15 / 191 (7.85%)
occurrences (all)	12	12	20
Haematoma			
subjects affected / exposed	1 / 160 (0.63%)	7 / 189 (3.70%)	10 / 191 (5.24%)
occurrences (all)	1	9	12
Flushing			
subjects affected / exposed	5 / 160 (3.13%)	12 / 189 (6.35%)	6 / 191 (3.14%)
occurrences (all)	5	15	6
Deep vein thrombosis			
subjects affected / exposed	15 / 160 (9.38%)	13 / 189 (6.88%)	4 / 191 (2.09%)
occurrences (all)	16	14	4
Hot flush			
subjects affected / exposed	2 / 160 (1.25%)	14 / 189 (7.41%)	4 / 191 (2.09%)
occurrences (all)	2	15	4
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	20 / 160 (12.50%)	29 / 189 (15.34%)	33 / 191 (17.28%)
occurrences (all)	22	43	45
Peripheral swelling			
subjects affected / exposed	8 / 160 (5.00%)	12 / 189 (6.35%)	17 / 191 (8.90%)
occurrences (all)	12	14	23
Oedema peripheral			
subjects affected / exposed	52 / 160 (32.50%)	64 / 189 (33.86%)	106 / 191 (55.50%)
occurrences (all)	71	103	170
Non-cardiac chest pain			
subjects affected / exposed	2 / 160 (1.25%)	10 / 189 (5.29%)	14 / 191 (7.33%)
occurrences (all)	2	11	17
Malaise			
subjects affected / exposed	3 / 160 (1.88%)	16 / 189 (8.47%)	17 / 191 (8.90%)
occurrences (all)	4	18	18
Influenza like illness			
subjects affected / exposed	4 / 160 (2.50%)	11 / 189 (5.82%)	16 / 191 (8.38%)
occurrences (all)	4	13	23
Fatigue			
subjects affected / exposed	53 / 160 (33.13%)	52 / 189 (27.51%)	69 / 191 (36.13%)
occurrences (all)	71	80	115
Chills			
subjects affected / exposed	10 / 160 (6.25%)	7 / 189 (3.70%)	12 / 191 (6.28%)
occurrences (all)	12	7	15
Asthenia			
subjects affected / exposed	44 / 160 (27.50%)	53 / 189 (28.04%)	58 / 191 (30.37%)
occurrences (all)	56	76	84
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	6 / 160 (3.75%)	7 / 189 (3.70%)	15 / 191 (7.85%)
occurrences (all)	6	7	17
Productive cough			
subjects affected / exposed	8 / 160 (5.00%)	5 / 189 (2.65%)	12 / 191 (6.28%)
occurrences (all)	8	7	13
Oropharyngeal pain			

subjects affected / exposed	4 / 160 (2.50%)	12 / 189 (6.35%)	12 / 191 (6.28%)
occurrences (all)	5	12	19
Hiccups			
subjects affected / exposed	6 / 160 (3.75%)	10 / 189 (5.29%)	5 / 191 (2.62%)
occurrences (all)	10	19	6
Epistaxis			
subjects affected / exposed	11 / 160 (6.88%)	16 / 189 (8.47%)	12 / 191 (6.28%)
occurrences (all)	13	20	14
Dyspnoea exertional			
subjects affected / exposed	7 / 160 (4.38%)	14 / 189 (7.41%)	12 / 191 (6.28%)
occurrences (all)	7	16	15
Dyspnoea			
subjects affected / exposed	32 / 160 (20.00%)	26 / 189 (13.76%)	39 / 191 (20.42%)
occurrences (all)	39	36	64
Dysphonia			
subjects affected / exposed	4 / 160 (2.50%)	12 / 189 (6.35%)	4 / 191 (2.09%)
occurrences (all)	4	16	4
Cough			
subjects affected / exposed	24 / 160 (15.00%)	37 / 189 (19.58%)	53 / 191 (27.75%)
occurrences (all)	26	50	85
Psychiatric disorders			
Agitation			
subjects affected / exposed	3 / 160 (1.88%)	10 / 189 (5.29%)	11 / 191 (5.76%)
occurrences (all)	3	11	13
Anxiety			
subjects affected / exposed	15 / 160 (9.38%)	25 / 189 (13.23%)	26 / 191 (13.61%)
occurrences (all)	17	35	32
Confusional state			
subjects affected / exposed	15 / 160 (9.38%)	11 / 189 (5.82%)	11 / 191 (5.76%)
occurrences (all)	18	13	11
Irritability			
subjects affected / exposed	3 / 160 (1.88%)	11 / 189 (5.82%)	4 / 191 (2.09%)
occurrences (all)	3	13	4
Insomnia			
subjects affected / exposed	27 / 160 (16.88%)	68 / 189 (35.98%)	70 / 191 (36.65%)
occurrences (all)	33	85	84

Depression			
subjects affected / exposed	10 / 160 (6.25%)	14 / 189 (7.41%)	26 / 191 (13.61%)
occurrences (all)	10	15	29
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 160 (0.63%)	4 / 189 (2.12%)	10 / 191 (5.24%)
occurrences (all)	1	5	12
Blood creatinine increased			
subjects affected / exposed	8 / 160 (5.00%)	12 / 189 (6.35%)	16 / 191 (8.38%)
occurrences (all)	9	18	18
Neutrophil count decreased			
subjects affected / exposed	11 / 160 (6.88%)	13 / 189 (6.88%)	18 / 191 (9.42%)
occurrences (all)	17	45	47
Platelet count decreased			
subjects affected / exposed	6 / 160 (3.75%)	4 / 189 (2.12%)	15 / 191 (7.85%)
occurrences (all)	13	4	40
Weight decreased			
subjects affected / exposed	20 / 160 (12.50%)	30 / 189 (15.87%)	35 / 191 (18.32%)
occurrences (all)	24	40	51
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	7 / 160 (4.38%)	20 / 189 (10.58%)	19 / 191 (9.95%)
occurrences (all)	7	25	23
Fall			
subjects affected / exposed	9 / 160 (5.63%)	35 / 189 (18.52%)	45 / 191 (23.56%)
occurrences (all)	10	67	68
Procedural pain			
subjects affected / exposed	2 / 160 (1.25%)	11 / 189 (5.82%)	6 / 191 (3.14%)
occurrences (all)	2	11	6
Skin laceration			
subjects affected / exposed	4 / 160 (2.50%)	10 / 189 (5.29%)	8 / 191 (4.19%)
occurrences (all)	5	10	10
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	8 / 160 (5.00%)	11 / 189 (5.82%)	7 / 191 (3.66%)
occurrences (all)	9	12	7

Cardiac failure			
subjects affected / exposed	3 / 160 (1.88%)	2 / 189 (1.06%)	1 / 191 (0.52%)
occurrences (all)	3	2	1
Palpitations			
subjects affected / exposed	1 / 160 (0.63%)	8 / 189 (4.23%)	11 / 191 (5.76%)
occurrences (all)	1	8	13
Nervous system disorders			
Tremor			
subjects affected / exposed	23 / 160 (14.38%)	27 / 189 (14.29%)	19 / 191 (9.95%)
occurrences (all)	27	39	20
Syncope			
subjects affected / exposed	2 / 160 (1.25%)	6 / 189 (3.17%)	14 / 191 (7.33%)
occurrences (all)	2	8	20
Sciatica			
subjects affected / exposed	3 / 160 (1.88%)	11 / 189 (5.82%)	16 / 191 (8.38%)
occurrences (all)	3	12	18
Peripheral sensory neuropathy			
subjects affected / exposed	27 / 160 (16.88%)	57 / 189 (30.16%)	85 / 191 (44.50%)
occurrences (all)	29	93	152
Paraesthesia			
subjects affected / exposed	13 / 160 (8.13%)	21 / 189 (11.11%)	25 / 191 (13.09%)
occurrences (all)	14	33	34
Neuropathy peripheral			
subjects affected / exposed	3 / 160 (1.88%)	9 / 189 (4.76%)	14 / 191 (7.33%)
occurrences (all)	3	11	16
Memory impairment			
subjects affected / exposed	3 / 160 (1.88%)	10 / 189 (5.29%)	7 / 191 (3.66%)
occurrences (all)	3	10	11
Hypoaesthesia			
subjects affected / exposed	7 / 160 (4.38%)	11 / 189 (5.82%)	14 / 191 (7.33%)
occurrences (all)	7	16	17
Headache			
subjects affected / exposed	22 / 160 (13.75%)	36 / 189 (19.05%)	33 / 191 (17.28%)
occurrences (all)	25	50	46
Dysgeusia			

subjects affected / exposed	14 / 160 (8.75%)	12 / 189 (6.35%)	32 / 191 (16.75%)
occurrences (all)	15	13	35
Dizziness			
subjects affected / exposed	31 / 160 (19.38%)	36 / 189 (19.05%)	31 / 191 (16.23%)
occurrences (all)	38	75	42
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	56 / 160 (35.00%)	51 / 189 (26.98%)	58 / 191 (30.37%)
occurrences (all)	92	85	107
Thrombocytopenia			
subjects affected / exposed	15 / 160 (9.38%)	14 / 189 (7.41%)	24 / 191 (12.57%)
occurrences (all)	30	25	41
Neutropenia			
subjects affected / exposed	36 / 160 (22.50%)	48 / 189 (25.40%)	39 / 191 (20.42%)
occurrences (all)	92	135	99
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 160 (0.00%)	6 / 189 (3.17%)	10 / 191 (5.24%)
occurrences (all)	0	7	11
Vertigo			
subjects affected / exposed	4 / 160 (2.50%)	18 / 189 (9.52%)	22 / 191 (11.52%)
occurrences (all)	4	21	26
Eye disorders			
Cataract			
subjects affected / exposed	6 / 160 (3.75%)	41 / 189 (21.69%)	54 / 191 (28.27%)
occurrences (all)	7	55	74
Dry eye			
subjects affected / exposed	1 / 160 (0.63%)	6 / 189 (3.17%)	17 / 191 (8.90%)
occurrences (all)	1	7	19
Vision blurred			
subjects affected / exposed	6 / 160 (3.75%)	22 / 189 (11.64%)	25 / 191 (13.09%)
occurrences (all)	6	22	26
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	6 / 160 (3.75%)	11 / 189 (5.82%)	11 / 191 (5.76%)
occurrences (all)	6	14	14
Abdominal pain			

subjects affected / exposed	10 / 160 (6.25%)	38 / 189 (20.11%)	30 / 191 (15.71%)
occurrences (all)	15	48	44
Abdominal pain upper			
subjects affected / exposed	13 / 160 (8.13%)	29 / 189 (15.34%)	23 / 191 (12.04%)
occurrences (all)	13	39	27
Constipation			
subjects affected / exposed	61 / 160 (38.13%)	82 / 189 (43.39%)	92 / 191 (48.17%)
occurrences (all)	78	128	120
Dental caries			
subjects affected / exposed	2 / 160 (1.25%)	11 / 189 (5.82%)	6 / 191 (3.14%)
occurrences (all)	2	15	8
Diarrhoea			
subjects affected / exposed	48 / 160 (30.00%)	115 / 189 (60.85%)	147 / 191 (76.96%)
occurrences (all)	82	292	378
Nausea			
subjects affected / exposed	35 / 160 (21.88%)	63 / 189 (33.33%)	78 / 191 (40.84%)
occurrences (all)	49	100	128
Dyspepsia			
subjects affected / exposed	16 / 160 (10.00%)	22 / 189 (11.64%)	21 / 191 (10.99%)
occurrences (all)	17	34	29
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 160 (1.88%)	10 / 189 (5.29%)	13 / 191 (6.81%)
occurrences (all)	3	13	15
Haemorrhoids			
subjects affected / exposed	6 / 160 (3.75%)	15 / 189 (7.94%)	12 / 191 (6.28%)
occurrences (all)	7	16	13
Inguinal hernia			
subjects affected / exposed	0 / 160 (0.00%)	10 / 189 (5.29%)	5 / 191 (2.62%)
occurrences (all)	0	13	5
Dry mouth			
subjects affected / exposed	14 / 160 (8.75%)	12 / 189 (6.35%)	13 / 191 (6.81%)
occurrences (all)	15	14	16
Toothache			
subjects affected / exposed	4 / 160 (2.50%)	15 / 189 (7.94%)	8 / 191 (4.19%)
occurrences (all)	4	16	11
Stomatitis			

subjects affected / exposed	9 / 160 (5.63%)	8 / 189 (4.23%)	15 / 191 (7.85%)
occurrences (all)	9	9	21
Vomiting			
subjects affected / exposed	13 / 160 (8.13%)	33 / 189 (17.46%)	66 / 191 (34.55%)
occurrences (all)	23	53	170
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	8 / 160 (5.00%)	22 / 189 (11.64%)	31 / 191 (16.23%)
occurrences (all)	8	26	35
Alopecia			
subjects affected / exposed	3 / 160 (1.88%)	8 / 189 (4.23%)	13 / 191 (6.81%)
occurrences (all)	3	8	14
Urticaria			
subjects affected / exposed	1 / 160 (0.63%)	5 / 189 (2.65%)	10 / 191 (5.24%)
occurrences (all)	3	6	12
Rash papular			
subjects affected / exposed	8 / 160 (5.00%)	4 / 189 (2.12%)	12 / 191 (6.28%)
occurrences (all)	8	5	13
Rash maculo-papular			
subjects affected / exposed	18 / 160 (11.25%)	22 / 189 (11.64%)	43 / 191 (22.51%)
occurrences (all)	35	40	111
Rash macular			
subjects affected / exposed	3 / 160 (1.88%)	11 / 189 (5.82%)	27 / 191 (14.14%)
occurrences (all)	7	14	39
Rash erythematous			
subjects affected / exposed	10 / 160 (6.25%)	3 / 189 (1.59%)	18 / 191 (9.42%)
occurrences (all)	12	3	32
Rash			
subjects affected / exposed	9 / 160 (5.63%)	7 / 189 (3.70%)	18 / 191 (9.42%)
occurrences (all)	12	7	25
Pruritus			
subjects affected / exposed	13 / 160 (8.13%)	29 / 189 (15.34%)	37 / 191 (19.37%)
occurrences (all)	15	42	59
Night sweats			
subjects affected / exposed	9 / 160 (5.63%)	9 / 189 (4.76%)	5 / 191 (2.62%)
occurrences (all)	9	11	6

Erythema			
subjects affected / exposed	2 / 160 (1.25%)	20 / 189 (10.58%)	16 / 191 (8.38%)
occurrences (all)	2	21	21
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	29 / 160 (18.13%)	50 / 189 (26.46%)	50 / 191 (26.18%)
occurrences (all)	34	78	73
Osteoarthritis			
subjects affected / exposed	4 / 160 (2.50%)	13 / 189 (6.88%)	24 / 191 (12.57%)
occurrences (all)	4	16	25
Neck pain			
subjects affected / exposed	9 / 160 (5.63%)	25 / 189 (13.23%)	22 / 191 (11.52%)
occurrences (all)	9	26	25
Myalgia			
subjects affected / exposed	9 / 160 (5.63%)	24 / 189 (12.70%)	33 / 191 (17.28%)
occurrences (all)	13	32	40
Musculoskeletal pain			
subjects affected / exposed	0 / 160 (0.00%)	14 / 189 (7.41%)	13 / 191 (6.81%)
occurrences (all)	0	19	15
Musculoskeletal chest pain			
subjects affected / exposed	12 / 160 (7.50%)	27 / 189 (14.29%)	25 / 191 (13.09%)
occurrences (all)	14	33	31
Muscle spasms			
subjects affected / exposed	27 / 160 (16.88%)	50 / 189 (26.46%)	52 / 191 (27.23%)
occurrences (all)	38	82	96
Joint swelling			
subjects affected / exposed	1 / 160 (0.63%)	11 / 189 (5.82%)	12 / 191 (6.28%)
occurrences (all)	1	12	14
Bone pain			
subjects affected / exposed	10 / 160 (6.25%)	24 / 189 (12.70%)	20 / 191 (10.47%)
occurrences (all)	10	30	24
Back pain			
subjects affected / exposed	34 / 160 (21.25%)	67 / 189 (35.45%)	64 / 191 (33.51%)
occurrences (all)	36	101	90
Arthritis			

subjects affected / exposed	0 / 160 (0.00%)	4 / 189 (2.12%)	16 / 191 (8.38%)
occurrences (all)	0	5	17
Arthralgia			
subjects affected / exposed	23 / 160 (14.38%)	81 / 189 (42.86%)	76 / 191 (39.79%)
occurrences (all)	34	155	143
Muscular weakness			
subjects affected / exposed	12 / 160 (7.50%)	19 / 189 (10.05%)	18 / 191 (9.42%)
occurrences (all)	13	22	25
Pathological fracture			
subjects affected / exposed	5 / 160 (3.13%)	20 / 189 (10.58%)	10 / 191 (5.24%)
occurrences (all)	7	23	11
Pain in jaw			
subjects affected / exposed	3 / 160 (1.88%)	8 / 189 (4.23%)	10 / 191 (5.24%)
occurrences (all)	3	10	11
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	2 / 160 (1.25%)	5 / 189 (2.65%)	18 / 191 (9.42%)
occurrences (all)	2	9	20
Cellulitis			
subjects affected / exposed	5 / 160 (3.13%)	3 / 189 (1.59%)	11 / 191 (5.76%)
occurrences (all)	5	3	15
Bronchitis			
subjects affected / exposed	13 / 160 (8.13%)	51 / 189 (26.98%)	74 / 191 (38.74%)
occurrences (all)	15	109	168
Cystitis			
subjects affected / exposed	2 / 160 (1.25%)	12 / 189 (6.35%)	13 / 191 (6.81%)
occurrences (all)	2	20	19
Urinary tract infection			
subjects affected / exposed	14 / 160 (8.75%)	27 / 189 (14.29%)	30 / 191 (15.71%)
occurrences (all)	18	44	56
Upper respiratory tract infection			
subjects affected / exposed	17 / 160 (10.63%)	47 / 189 (24.87%)	48 / 191 (25.13%)
occurrences (all)	29	88	97
Tooth infection			
subjects affected / exposed	2 / 160 (1.25%)	11 / 189 (5.82%)	10 / 191 (5.24%)
occurrences (all)	2	24	10

Sinusitis			
subjects affected / exposed	1 / 160 (0.63%)	6 / 189 (3.17%)	18 / 191 (9.42%)
occurrences (all)	1	7	24
Pneumonia			
subjects affected / exposed	6 / 160 (3.75%)	20 / 189 (10.58%)	24 / 191 (12.57%)
occurrences (all)	6	21	31
Pharyngitis			
subjects affected / exposed	1 / 160 (0.63%)	10 / 189 (5.29%)	10 / 191 (5.24%)
occurrences (all)	1	13	11
Nasopharyngitis			
subjects affected / exposed	13 / 160 (8.13%)	71 / 189 (37.57%)	62 / 191 (32.46%)
occurrences (all)	16	137	133
Influenza			
subjects affected / exposed	3 / 160 (1.88%)	22 / 189 (11.64%)	13 / 191 (6.81%)
occurrences (all)	3	24	18
Herpes zoster			
subjects affected / exposed	4 / 160 (2.50%)	4 / 189 (2.12%)	24 / 191 (12.57%)
occurrences (all)	4	4	27
Gastroenteritis			
subjects affected / exposed	4 / 160 (2.50%)	15 / 189 (7.94%)	15 / 191 (7.85%)
occurrences (all)	4	21	18
Rhinitis			
subjects affected / exposed	5 / 160 (3.13%)	21 / 189 (11.11%)	23 / 191 (12.04%)
occurrences (all)	5	31	29
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	45 / 160 (28.13%)	35 / 189 (18.52%)	45 / 191 (23.56%)
occurrences (all)	55	47	69
Dehydration			
subjects affected / exposed	11 / 160 (6.88%)	5 / 189 (2.65%)	12 / 191 (6.28%)
occurrences (all)	14	7	18
Gout			
subjects affected / exposed	4 / 160 (2.50%)	14 / 189 (7.41%)	10 / 191 (5.24%)
occurrences (all)	5	24	19
Hyperglycaemia			

subjects affected / exposed	3 / 160 (1.88%)	15 / 189 (7.94%)	6 / 191 (3.14%)
occurrences (all)	3	20	8
Hypocalcaemia			
subjects affected / exposed	13 / 160 (8.13%)	12 / 189 (6.35%)	4 / 191 (2.09%)
occurrences (all)	19	13	5
Hypokalaemia			
subjects affected / exposed	16 / 160 (10.00%)	33 / 189 (17.46%)	39 / 191 (20.42%)
occurrences (all)	25	50	67
Hypomagnesaemia			
subjects affected / exposed	8 / 160 (5.00%)	11 / 189 (5.82%)	15 / 191 (7.85%)
occurrences (all)	16	16	23
Hyponatraemia			
subjects affected / exposed	6 / 160 (3.75%)	7 / 189 (3.70%)	4 / 191 (2.09%)
occurrences (all)	6	8	5
Hypophosphataemia			
subjects affected / exposed	2 / 160 (1.25%)	3 / 189 (1.59%)	9 / 191 (4.71%)
occurrences (all)	4	8	10

Non-serious adverse events	Ixazomib+ LenDex (Exposure Up to 18 Cycles)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	162 / 163 (99.39%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 163 (3.68%)		
occurrences (all)	7		
Hypotension			
subjects affected / exposed	17 / 163 (10.43%)		
occurrences (all)	19		
Haematoma			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences (all)	2		
Flushing			
subjects affected / exposed	4 / 163 (2.45%)		
occurrences (all)	5		
Deep vein thrombosis			

subjects affected / exposed	5 / 163 (3.07%)		
occurrences (all)	5		
Hot flush			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	30 / 163 (18.40%)		
occurrences (all)	53		
Peripheral swelling			
subjects affected / exposed	8 / 163 (4.91%)		
occurrences (all)	8		
Oedema peripheral			
subjects affected / exposed	66 / 163 (40.49%)		
occurrences (all)	91		
Non-cardiac chest pain			
subjects affected / exposed	4 / 163 (2.45%)		
occurrences (all)	4		
Malaise			
subjects affected / exposed	6 / 163 (3.68%)		
occurrences (all)	6		
Influenza like illness			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	41 / 163 (25.15%)		
occurrences (all)	61		
Chills			
subjects affected / exposed	11 / 163 (6.75%)		
occurrences (all)	14		
Asthenia			
subjects affected / exposed	36 / 163 (22.09%)		
occurrences (all)	47		
Respiratory, thoracic and mediastinal disorders			

Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 163 (1.23%) 3		
Productive cough subjects affected / exposed occurrences (all)	2 / 163 (1.23%) 2		
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 163 (1.84%) 3		
Hiccups subjects affected / exposed occurrences (all)	2 / 163 (1.23%) 4		
Epistaxis subjects affected / exposed occurrences (all)	7 / 163 (4.29%) 8		
Dyspnoea exertional subjects affected / exposed occurrences (all)	8 / 163 (4.91%) 11		
Dyspnoea subjects affected / exposed occurrences (all)	21 / 163 (12.88%) 29		
Dysphonia subjects affected / exposed occurrences (all)	5 / 163 (3.07%) 5		
Cough subjects affected / exposed occurrences (all)	28 / 163 (17.18%) 33		
Psychiatric disorders Agitation subjects affected / exposed occurrences (all)	4 / 163 (2.45%) 4		
Anxiety subjects affected / exposed occurrences (all)	22 / 163 (13.50%) 22		
Confusional state			

subjects affected / exposed	16 / 163 (9.82%)		
occurrences (all)	19		
Irritability			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	30 / 163 (18.40%)		
occurrences (all)	36		
Depression			
subjects affected / exposed	18 / 163 (11.04%)		
occurrences (all)	19		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	2		
Blood creatinine increased			
subjects affected / exposed	6 / 163 (3.68%)		
occurrences (all)	6		
Neutrophil count decreased			
subjects affected / exposed	5 / 163 (3.07%)		
occurrences (all)	12		
Platelet count decreased			
subjects affected / exposed	6 / 163 (3.68%)		
occurrences (all)	7		
Weight decreased			
subjects affected / exposed	24 / 163 (14.72%)		
occurrences (all)	29		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 163 (1.84%)		
occurrences (all)	4		
Fall			
subjects affected / exposed	8 / 163 (4.91%)		
occurrences (all)	10		
Procedural pain			

subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Skin laceration			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences (all)	2		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 163 (3.68%)		
occurrences (all)	6		
Cardiac failure			
subjects affected / exposed	9 / 163 (5.52%)		
occurrences (all)	9		
Palpitations			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences (all)	2		
Nervous system disorders			
Tremor			
subjects affected / exposed	14 / 163 (8.59%)		
occurrences (all)	18		
Syncope			
subjects affected / exposed	4 / 163 (2.45%)		
occurrences (all)	4		
Sciatica			
subjects affected / exposed	4 / 163 (2.45%)		
occurrences (all)	5		
Peripheral sensory neuropathy			
subjects affected / exposed	23 / 163 (14.11%)		
occurrences (all)	31		
Paraesthesia			
subjects affected / exposed	9 / 163 (5.52%)		
occurrences (all)	10		
Neuropathy peripheral			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences (all)	2		
Memory impairment			

subjects affected / exposed occurrences (all) Hypoaesthesia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	4 / 163 (2.45%) 4 6 / 163 (3.68%) 7 15 / 163 (9.20%) 21 9 / 163 (5.52%) 12 27 / 163 (16.56%) 34		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	 51 / 163 (31.29%) 85 32 / 163 (19.63%) 77 15 / 163 (9.20%) 27		
Ear and labyrinth disorders Hypoacusis subjects affected / exposed occurrences (all) Vertigo subjects affected / exposed occurrences (all)	 1 / 163 (0.61%) 1 3 / 163 (1.84%) 3		
Eye disorders Cataract subjects affected / exposed occurrences (all) Dry eye	 1 / 163 (0.61%) 1		

subjects affected / exposed	5 / 163 (3.07%)		
occurrences (all)	5		
Vision blurred			
subjects affected / exposed	6 / 163 (3.68%)		
occurrences (all)	7		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	7 / 163 (4.29%)		
occurrences (all)	7		
Abdominal pain upper			
subjects affected / exposed	8 / 163 (4.91%)		
occurrences (all)	8		
Constipation			
subjects affected / exposed	59 / 163 (36.20%)		
occurrences (all)	71		
Dental caries			
subjects affected / exposed	0 / 163 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	68 / 163 (41.72%)		
occurrences (all)	115		
Nausea			
subjects affected / exposed	55 / 163 (33.74%)		
occurrences (all)	77		
Dyspepsia			
subjects affected / exposed	5 / 163 (3.07%)		
occurrences (all)	6		
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 163 (2.45%)		
occurrences (all)	5		
Haemorrhoids			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		

Inguinal hernia subjects affected / exposed occurrences (all)	0 / 163 (0.00%) 0			
Dry mouth subjects affected / exposed occurrences (all)	11 / 163 (6.75%) 11			
Toothache subjects affected / exposed occurrences (all)	3 / 163 (1.84%) 4			
Stomatitis subjects affected / exposed occurrences (all)	10 / 163 (6.13%) 10			
Vomiting subjects affected / exposed occurrences (all)	41 / 163 (25.15%) 59			
Skin and subcutaneous tissue disorders				
Dry skin subjects affected / exposed occurrences (all)	11 / 163 (6.75%) 13			
Alopecia subjects affected / exposed occurrences (all)	3 / 163 (1.84%) 4			
Urticaria subjects affected / exposed occurrences (all)	2 / 163 (1.23%) 2			
Rash papular subjects affected / exposed occurrences (all)	8 / 163 (4.91%) 12			
Rash maculo-papular subjects affected / exposed occurrences (all)	37 / 163 (22.70%) 69			
Rash macular subjects affected / exposed occurrences (all)	11 / 163 (6.75%) 27			
Rash erythematous				

subjects affected / exposed	6 / 163 (3.68%)		
occurrences (all)	10		
Rash			
subjects affected / exposed	11 / 163 (6.75%)		
occurrences (all)	11		
Pruritus			
subjects affected / exposed	16 / 163 (9.82%)		
occurrences (all)	23		
Night sweats			
subjects affected / exposed	9 / 163 (5.52%)		
occurrences (all)	10		
Erythema			
subjects affected / exposed	11 / 163 (6.75%)		
occurrences (all)	14		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	18 / 163 (11.04%)		
occurrences (all)	24		
Osteoarthritis			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	7 / 163 (4.29%)		
occurrences (all)	9		
Myalgia			
subjects affected / exposed	5 / 163 (3.07%)		
occurrences (all)	10		
Musculoskeletal pain			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	12 / 163 (7.36%)		
occurrences (all)	13		
Muscle spasms			

subjects affected / exposed	15 / 163 (9.20%)		
occurrences (all)	21		
Joint swelling			
subjects affected / exposed	7 / 163 (4.29%)		
occurrences (all)	7		
Bone pain			
subjects affected / exposed	4 / 163 (2.45%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	26 / 163 (15.95%)		
occurrences (all)	30		
Arthritis			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	23 / 163 (14.11%)		
occurrences (all)	31		
Muscular weakness			
subjects affected / exposed	9 / 163 (5.52%)		
occurrences (all)	13		
Pathological fracture			
subjects affected / exposed	7 / 163 (4.29%)		
occurrences (all)	8		
Pain in jaw			
subjects affected / exposed	5 / 163 (3.07%)		
occurrences (all)	5		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences (all)	2		
Cellulitis			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences (all)	3		
Bronchitis			
subjects affected / exposed	13 / 163 (7.98%)		
occurrences (all)	14		

Cystitis				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences (all)	2			
Urinary tract infection				
subjects affected / exposed	19 / 163 (11.66%)			
occurrences (all)	33			
Upper respiratory tract infection				
subjects affected / exposed	10 / 163 (6.13%)			
occurrences (all)	14			
Tooth infection				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences (all)	2			
Sinusitis				
subjects affected / exposed	5 / 163 (3.07%)			
occurrences (all)	5			
Pneumonia				
subjects affected / exposed	7 / 163 (4.29%)			
occurrences (all)	7			
Pharyngitis				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences (all)	2			
Nasopharyngitis				
subjects affected / exposed	13 / 163 (7.98%)			
occurrences (all)	16			
Influenza				
subjects affected / exposed	3 / 163 (1.84%)			
occurrences (all)	3			
Herpes zoster				
subjects affected / exposed	4 / 163 (2.45%)			
occurrences (all)	4			
Gastroenteritis				
subjects affected / exposed	4 / 163 (2.45%)			
occurrences (all)	4			
Rhinitis				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences (all)	2			

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	34 / 163 (20.86%)		
occurrences (all)	39		
Dehydration			
subjects affected / exposed	10 / 163 (6.13%)		
occurrences (all)	13		
Gout			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	7 / 163 (4.29%)		
occurrences (all)	12		
Hypocalcaemia			
subjects affected / exposed	6 / 163 (3.68%)		
occurrences (all)	10		
Hypokalaemia			
subjects affected / exposed	33 / 163 (20.25%)		
occurrences (all)	46		
Hypomagnesaemia			
subjects affected / exposed	6 / 163 (3.68%)		
occurrences (all)	6		
Hyponatraemia			
subjects affected / exposed	10 / 163 (6.13%)		
occurrences (all)	27		
Hypophosphataemia			
subjects affected / exposed	9 / 163 (5.52%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2019	The following changes were implemented as per Amendment 4: 1. Updated statistical procedures to modify the number of events for the final PFS analysis. 2. Clarified the statistical boundary for PFS at the second IA. 3. Clarified that REVLIMID or generic lenalidomide may be administered as part of the study treatment regimen. 4. Removed the requirement to document adverse events that require breaking the blind in the eCRF. 5. Updated the SAE reporting contact information in Japan to BI Medical. 6. Clarified the duration of new primary malignancy AE assessment. 7. Clarified the locations of study centers.
09 July 2020	The following changes were implemented as per Amendment 5: 1. Added language to clarify ongoing treatment of participants—participants should be moved off study and onto commercial supply of ixazomib and/or lenalidomide, if available, and otherwise kept on study. 2. Updated Schedule of Events. 3. Revised Study Period Definitions. 4. Added explanatory text to Study Objectives. 5. Added explanatory text to Study Endpoints. 6. Added explanatory text to Overview of Study Design and removed language regarding the previous Schedule of Events. 7. Revised information regarding the interim analyses in the Overview of Study Design. 8. Revised thrombocytopenia text in Management of Clinical Events. 9. Revised Blinding and Unblinding text. 10. Revised language in Preparation, Reconstitution, and Dispensing. 11. Added a sentence to Packaging and Labeling. 12. Added language in Storage, Handling, and Accountability. 13. Added language regarding alternative methods for administering study procedures/assessments when it is not possible for the patient to come to the study site due to extenuating circumstances (eg, due to the COVID-19 pandemic). 14. Removed or revised several study procedures. 15. Revised language regarding unscheduled visits. 16. Revised language regarding completion of treatment. 17. Revised language regarding completion of study. 18. Revised language regarding discontinuation of treatment with the study drug regimen, and patient replacement. 19. Revised language regarding withdrawal of patients from study. 20. Revised language regarding statistical and quantitative analyses. 22. Added language to Independent Review Committee section. 23. Added language to Procedures for Recording and Reporting Adverse Events and Serious Adverse Events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported